

Institution: **US PATENT & TRADEMARK OFFICE** Sign In as Member/Individual*Journal of Clinical Oncology*, Vol 18, Issue 20 (October),
2000: 3513-3521

© 2000 American Society for Clinical Oncology

Homoharringtonine and Low-Dose Cytarabine in the Management of Late Chronic-Phase Chronic Myelogenous Leukemia

By Hagop M. Kantarjian, Moshe Talpaz, Terry L. Smith, Jorge Cortes, Francis J. Giles, Mary Beth Rios, Susie Mallard, James Gajewski, Anthony Murgo, Bruce Cheson, Susan O'Brien

From the Departments of Leukemia, Bioimmunotherapy, Biostatistics, and Blood and Bone Marrow Transplantation, M.D. Anderson Cancer Center, Houston, TX; and the National Cancer Institute, Bethesda, MD.

Address reprint requests to Hagop M. Kantarjian, MD, Department of Leukemia, Box 61, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; emailhkantarj@mdanderson.org.

This Article

- ▶ **Abstract FREE**
- ▶ **Full Text (PDF)**
- ▶ **Alert me when this article is cited**
- ▶ **Alert me if a correction is posted**

Services

- ▶ **Email this article to a colleague**
- ▶ **Similar articles in this journal**
- ▶ **Similar articles in PubMed**
- ▶ **Alert me to new issues of the journal**
- ▶ **Save to my personal folders**
- ▶ **Download to citation manager**
- ▶ **Cited by other online articles**

Google Scholar

- ▶ **Articles by Kantarjian, H. M.**
- ▶ **Articles by O'Brien, S.**
- ▶ **Articles citing this Article**

PubMed

- ▶ **PubMed Citation**
- ▶ **Articles by Kantarjian, H. M.**
- ▶ **Articles by O'Brien, S.**

► ABSTRACT

PURPOSE: : To evaluate the efficacy and toxicity profiles of a combination regimen of homoharringtonine (HHT) and low-dose cytarabine (ara-C) in patients with Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia (CML) who had experienced treatment failure with interferon alfa (IFN α) therapy.

PATIENTS AND METHODS: One hundred five patients were treated: 100 in chronic phase (15 with cytogenetic clonal evolution) and five in accelerated phase. Their median age was 52 years; all had been treated unsuccessfully with IFN α ; 94% were in late chronic phase; 43% had been exposed to ara-C and 11% had been exposed to HHT. Patients received HHT 2.5 mg/m² by continuous infusion daily for 5 days and ara-C 15 mg/m² daily in two subcutaneous injections for 5 days every 4 weeks. The outcome of the 100 patients in chronic phase was compared with

- ▲ **TOP**
- **ABSTRACT**
- ▼ **INTRODUCTION**
- ▼ **PATIENTS AND METHODS**
- ▼ **RESULTS**
- ▼ **DISCUSSION**
- ▼ **REFERENCES**

a previous study group of 73 patients treated with HHT alone.

RESULTS: Overall, the complete hematologic response (CHR) rate in chronic phase was 72%; the cytogenetic response rate was 32% (major response, 15%; complete response, 5%). Toxicities were acceptable, mostly related to moderate diarrhea (3%), headaches (3%), cardiovascular events (3%), and myelosuppression-associated complications (3% to 14%). With a median follow-up period of 25 months, the estimated 4-year survival rate was 55%. Response rates were identical with HHT plus ara-C versus HHT alone, but the survival was significantly longer with the combination after accounting for differences in the study groups and by multivariate analysis.

CONCLUSION: The combination regimen of HHT and ara-C is effective and safe in patients with CML who have experienced treatment failure with IFN α and needs to be investigated together with IFN α as part of front-line CML therapy. The addition of ara-C did not improve the response rates but may have improved survival, perhaps through suppression of clones related to disease transformation.

► INTRODUCTION

SURVIVAL IN Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia (CML) has improved with interferon alfa (IFN α) therapy and allogeneic stem-cell transplantation (SCT).¹⁻⁴ With IFN α regimens, the median survival is 6 to 7 years. Prognosis is associated with patient risk group,^{5,6} dose schedules of IFN α , combined therapies (eg, with low-dose cytarabine [ara-C]),⁷⁻⁹ and the achievement and degree of Ph-suppression (cytogenetic response). By multivariate and landmark analyses, achievement of cytogenetic and major cytogenetic responses (Ph-positive metaphases < 35%) have been associated independently with survival prolongation.⁸⁻¹²

▲ TOP
▲ ABSTRACT
▪ INTRODUCTION
▼ PATIENTS AND METHODS
▼ RESULTS
▼ DISCUSSION
▼ REFERENCES

Improving on the state and duration of minimal disease burden (complete hematologic or cytogenetic response) in CML, as in other cancers, has become the target of many investigational strategies and a surrogate end point for long-term survival. Discovering agents or modalities that may suppress Ph-positive cells is thus actively pursued. Patients who fail IFN α regimens and who are not eligible for allogeneic SCT have the option of receiving hydroxyurea therapy or undergoing investigational approaches such as autologous SCT or new agents.

Homoharringtonine (HHT), a plant alkaloid, was first investigated in China and reported to be active in leukemias.^{13,14} Phase I and II studies in the United States confirmed its antileukemic activity but documented a high incidence of cardiovascular complications with short-infusion schedules^{15,16} and with higher-dose continuous-infusion schedules (30% incidence of hypotension and arrhythmias).¹⁷ However, definite activity was observed in acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), and myelodysplastic syndrome (MDS).¹⁷⁻²⁰ We had investigated a lower-dose, longer-duration, continuous-infusion schedule of HHT (2.5 mg/m² daily for 10 to 14 days instead of 5 to 9 mg/m² daily for 5 to 7 days). This schedule abrogated the occurrence of cardiovascular complications including hypotensive events and arrhythmias, which occurred in less than 5% of patients with the new schedule.²⁰ This observation, together with the noted antiproliferative effect of HHT, resulted in further studies of the new schedule in CML, an indolent disease that requires a safe schedule for long-term therapy. We subsequently reported on the efficacy of HHT alone in patients

with late chronic-phase CML (duration of disease more than 12 months), many of whom were IFN α -resistant, and in sequence with IFN α in early chronic-phase CML.^{21,22} In both studies, significant anti-CML efficacy was observed.

ara-C has shown activity in CML as a single agent and in combination with IFN α .²³⁻²⁵ The mechanisms underlying the anti-CML efficacy of HHT are unknown but may be mediated through an effect on the apoptosis pathways.^{26,27} HHT had also been reported to be synergistic with IFN α and with ara-C in preclinical models.²⁷ The limited therapeutic options of patients with late chronic-phase CML who experience treatment failure with IFN α therapy and who are not candidates for allogeneic SCT and the efficacy of both HHT and ara-C *in vitro*²⁶⁻²⁸ and *in vivo*²¹⁻²⁵ led to the current investigation of HHT and low-dose ara-C combination in patients who have failed IFN α regimens. The results are summarized in this study.

► PATIENTS AND METHODS

Study Group

Adults with a diagnosis of Ph-positive CML were entered onto the study after informed consent was obtained. Eligibility criteria were as follows: (1) age 15 years or older, (2) chronic- or accelerated-phase CML disease,²⁹ (3) good performance status (Zubrod 0 to 2), (4) treatment failure on an IFN α -containing regimen, (5) normal renal (creatinine < 2 mg/dL) and hepatic functions (bilirubin < 2 mg/dL), and (6) no evidence of severe cardiac disease (class III or IV).

▲ TOP
▲ ABSTRACT
▲ INTRODUCTION
• PATIENTS AND METHODS
▼ RESULTS
▼ DISCUSSION
▼ REFERENCES

Treatment failure of IFN α -containing regimens was defined in one of three categories: (1) hematologic resistance referred to failure to achieve at least a partial hematologic response (PHR) after 3 months or more of therapy, failure to achieve a complete hematologic response (CHR) after 6 months or more of therapy, or loss of hematologic response after achieving CHR, with an increasing WBC count greater than $12 \times 10^9/L$ on optimal IFN α therapy documented for at least 4 weeks; (2) cytogenetic resistance referred to failure to obtain a cytogenetic response (Ph-positive cells $\geq 90\%$) after 12 months or more of therapy, or loss of cytogenetic response with return of Ph-positive cells to greater than 90%; and (3) severe grade 3 or 4 unacceptable toxicity related to IFN α therapy. For hematologic or cytogenetic resistance, patients were required to have received IFN α at 5 million U/m² daily or the maximum-tolerated dose. The median IFN α dose delivery in our studies was 5 million U/m² daily with IFN α alone and more than 3 million U/m² daily with IFN α combinations. In the category of failure because of unacceptable IFN α -associated toxicity, no minimum dose or duration of therapy was specified, because some of these toxicities may not be dose-related and are life-threatening (eg, immune-mediated thrombocytopenia, immune-mediated hemolysis, neurotoxicity, severe depression, cardiomyopathy, pulmonary failure, and so on).

Patients in blastic phase were not eligible (marrow or peripheral blasts $\geq 30\%$). Patients with cytogenetic clonal evolution as their only accelerated-phase feature were included in the chronic-phase analysis on the basis of their more favorable prognosis from previous analyses.^{30,31} Late chronic phase of CML was defined as time from diagnosis to start of therapy of more than 12 months.^{1,2,6,9,25}

Characteristics of the study group are listed in Table 1. Their median age was 52 years; 49% were females. All patients had previously received IFN α therapy; 54% were referred from outside the institution having experienced treatment failure with IFN α . IFN α treatment failure was attributed to

hematologic resistance (42 patients), lack of cytogenetic response after 12 months or more of IFN α (25 patients), severe unacceptable toxicity with IFN α (18 patients), resistance plus toxicity (16 patients), or other reasons (four patients). All 25 patients entered for lack of cytogenetic response had IFN α therapy discontinued and had evidence of active CML disease (leukocytosis, thrombocytosis) at the time of initiation of HHT and ara-C therapy. Only six patients received therapy with a CML chronic-phase duration of less than 12 months: five had IFN α therapy discontinued because of severe toxicities (two of them with resistance) and one because of hematologic resistance. Eleven patients had previously received HHT on the front-line sequential HHT followed by IFN α maintenance (DM91-13)²²; 45 patients had previously received ara-C with IFN α .

View this table: Table 1. Characteristics of the Study Group (105 patients)

[in this window]

[in a new window]

All 105 patients had 95% to 100% Ph-positive metaphases at the start of HHT and ara-C therapy. One hundred patients were in chronic phase, 15 of whom had cytogenetic clonal evolution. This included trisomy 8 (two patients), double Philadelphia (one patient), isochromosome 17 (one patient), and other abnormalities (11 patients). Five patients had accelerated phase CML (basophilia $\geq 20\%$, two patients; blasts $\geq 15\%$, one patient; thrombocytopenia $< 100 \times 10^9/L$, two patients).

Therapy

HHT was given at a dose of 2.5 mg/m^2 by continuous infusion daily for 5 days (days 1 to 5) together with ara-C 15 mg/m^2 daily in two equal subcutaneous doses 12 hours apart for 5 days (days 1 to 5). HHT was given either through a central-line catheter or through a peripheral-line catheter replaced every 2 to 3 days. Therapy was repeated every 4 weeks. HHT and ara-C therapy was modified to achieve with each course a lowest granulocyte count of approximately $10^9/L$, with a platelet count greater than $50 \times 10^9/L$. For this purpose, the modifications in therapy were in the duration of treatment, ie, in the number of days of treatment (± 1 day), rather than in the daily dose of HHT or ara-C. For example, a patient who had achieved a lowest granulocyte count greater than $2 \times 10^9/L$ and lowest platelet count greater than $100 \times 10^9/L$ on a course of HHT and ara-C given for n days will receive the next course of HHT and ara-C for $(n + 1)$ days. In contrast, a patient who had achieved a lowest granulocyte count of less than $10^9/L$ or a lowest platelet count of less than $50 \times 10^9/L$ on a course given for n days will receive the next course of HHT and ara-C for $(n - 1)$ days.

Therapy was discontinued for the following reasons: (1) evidence of resistance with the optimal acceptable dose schedule, (2) disease transformation, (3) unacceptable toxicity (grade 3 to 4) after dose reductions were made, (4) availability of other better options (eg, allogeneic SCT), or (5) patient or physician choice (eg, in the case of a lack of cytogenetic response after 12 months of therapy). If toxicity was due to a particular agent (eg, hypotension or headache with HHT), then the daily dose in subsequent courses was reduced by 25% for grade 2 persistent toxicity and by 50% for grade 3 to 4 toxicities. Toxicity was graded according to the National Cancer Institute common toxicity criteria.³²

Criteria and Statistical Considerations

Response criteria were as previously described.^{2,6} A CHR required a WBC count of less than $10 \times 10^9/L$ without peripheral immature cells (blasts, promyelocytes, myelocytes), a platelet count of $450 \times 10^9/L$ or less, and disappearance of signs and symptoms of disease, including palpable splenomegaly. CHR was further classified by cytogenetic response based on best suppression of Ph-positive cells as

follows: complete, Ph-positive 0%; partial, Ph-positive 1% to 34%; and minor, Ph-positive 35% to 90%. A major cytogenetic response included complete and partial cytogenetic responses (Ph-positive < 35%). A PHR was defined as for CHR, but with persistence of peripheral immature cells and/or splenomegaly or thrombocytosis (but 50% or less of pretreatment).

Results of χ^2 tests are presented as an indication of association of pretreatment characteristics with cytogenetic response outcomes. Survival estimates were based on the method of Kaplan and Meier³³ and compared using the log-rank test.³⁴ For purposes of comparing results of this trial to those obtained on the trial that immediately preceded it,²¹ patients were classified into risk groups on the basis of a combination of four factors (age, performance status, interval from CML diagnosis to treatment, and percentage of peripheral basophils) previously reported as determinants of prognosis in late chronic-phase CML.³⁵

► RESULTS

Chronic-Phase CML

One hundred patients had chronic-phase CML; 15 of them had evidence of clonal evolution. All had evidence of active CML disease at the start of therapy (patients entered on therapy because of cytogenetic resistance had IFN α therapy discontinued and were exhibiting WBC or platelet count increases by the time HHT and ara-C therapy was started).

▲ TOP
▲ ABSTRACT
▲ INTRODUCTION
▲ PATIENTS AND METHODS
▪ RESULTS
▼ DISCUSSION
▼ REFERENCES

Among 85 patients with active chronic-phase disease but without clonal evolution, 61 (72%) achieved CHR, and 11 (13%) had PHR. Cytogenetic response was noted in 26 patients (31%): major in 12 (14%) and complete in four (5%) (Table 2).

View this table: Table 2. Response to Therapy in 105 Patients Treated

[in this window]

[in a new window]

Among 15 patients with evidence of clonal evolution, 11 (73%) achieved CHR, three (20%) achieved a PHR, and one failed to achieve a response. A cytogenetic response was observed in six of the 11 patients who had achieved CHR (55%; 40% of total); response was complete in one, partial in two, and minor in three patients. Clonal evolution disappeared in the patient achieving complete cytogenetic response and in two of three patients who had a minor cytogenetic response. One of the five patients who had CHR without Ph suppression also had complete suppression of the clonal evolution.

Accelerated-Phase CML

Among five patients treated in accelerated-phase CML, three (60%) obtained CHR. One such patient achieved a complete cytogenetic response.

Side Effects

Nonhematologic. Side effects of HHT and ara-C combination are listed in Table 3. The most common side effects were diarrhea and headache during therapy, mostly attributable to HHT. They were rarely severe (two patients; 2%). Other side effects such as skin rashes, nausea, vomiting, fatigue, and aches

were unusual. Of note, hypotension and arrhythmias were observed in only 4% of patients.

View this table: Table 3. Side Effects

[\[in this window\]](#)

[\[in a new window\]](#)

Hematologic. With induction therapy, the incidence of granulocytopenia less than $0.5 \times 10^9/\text{L}$ was 13% and the incidence of thrombocytopenia less than $30 \times 10^9/\text{L}$ was 4%. Significant anemia with hemoglobin less than 9.0 g/dL occurred in 14% during induction and in 50% of patients (14% of courses) during maintenance therapy.

Prognosis by Pretreatment Characteristics

Responses in chronic phase by different pretreatment characteristics are listed in Table 4. No significant associations were found between cytogenetic response and known prognostic features. There were no differences in response by duration of chronic-phase disease or by prior exposure to ara-C. Survival was significantly worse among older patients. A trend for worse survival was also observed with thrombocytosis, increased marrow blasts, and longer duration of chronic phase (Table 4).

View this table: Table 4. Outcome Within Subsets Based on Pretreatment Characteristics

[\[in this window\]](#)

[\[in a new window\]](#)

Follow-Up Results

The median number of HHT and ara-C courses was nine (range, one to 50 courses). The total number of courses received so far was 1,071. With a median follow-up time of 25 months, 18 deaths have occurred, at times ranging from 5 to 39 months after the start of therapy. The estimated survival rates at 2 and 4 years were 77% and 55%, respectively (Fig 1). The median time on therapy was 10 months (Fig 2). At last follow-up, 41 patients continued on therapy, and 64 were removed from study for reasons listed in Table 5.

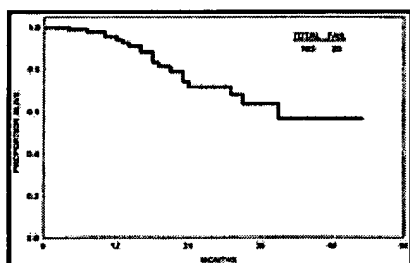


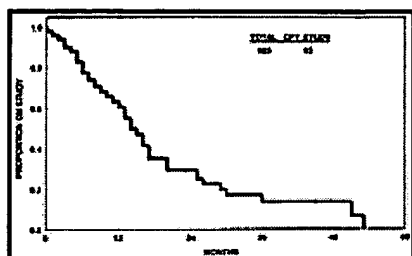
Fig1. Overall survival from start of

View larger version (11K):

[\[in this window\]](#)

[\[in a new window\]](#)

Fig2. Time on



View larger version (12K):

[\[in this window\]](#)

[\[in a new window\]](#)

View this table: Table 5. Patient Status (N = 105 Patients)

[\[in this window\]](#)

[\[in a new window\]](#)

The course of patients who achieved a major cytogenetic response is listed in Table 6. At the time of last follow-up, seven of the 16 patients with cytogenetic response (44%) continued to have a cytogenetic response: two were still in CHR on therapy, three developed hematologic resistance, and four were removed from study because of toxicity (two patients), patient request (one patient), and catheter-related problems (one patient). Two of 16 cytogenetic responders died (one after allogeneic transplantation) compared with 18 of 89 patients without a cytogenetic response.

View this table: Table 6. Follow-Up of Patients With Major Cytogenetic Response

[\[in this window\]](#)

[\[in a new window\]](#)

Comparison of HHT Plus Ara-C to Previous HHT alone

To evaluate the possible impact on survival of adding ara-C to HHT, we compared the results of the 100 patients in chronic phase for this trial with the previous trial of HHT alone, which accrued 73 patients with late chronic-phase CML. That trial was conducted starting in 1989 and had identical eligibility requirements to the HHT plus ara-C trial, except that there was no prior exposure to HHT or ara-C (not available then) and prior IFN α treatment failure was not required. Compared with the 100 patients in chronic phase receiving HHT plus ara-C, the patients treated with HHT alone were younger ($P = .07$), but had a higher incidence of splenomegaly ($P = .06$) and leukocytosis ($P = .002$) and a higher incidence of peripheral blasts ($P = .001$) and clonal evolution ($P = .03$) (Table 7).

View this table: Table 7. Comparison of HHT Versus HHT Plus Ara-C Study Group

[\[in this window\]](#)

[\[in a new window\]](#)

Although there were differences in distributions of patient characteristics between the two trials (Table 7), a categorization of patients into risk groups based on four factors previously identified as important for prognosis in late chronic-phase CML³⁵ suggested that patients on the two studies had similar overall

prognosis. A slightly higher proportion of patients receiving HHT alone fell in the lowest risk group, having none of the unfavorable factors (age ≥ 60 years, time from diagnosis to treatment ≥ 3 years, performance status of ≥ 1 , or peripheral-blood basophils $\geq 7\%$). Response rates were nearly identical on the two trials (Table 7), but early results suggested that survival was somewhat prolonged for patients treated with HHT plus ara-C (Fig 3; $P = .04$ [test stratified by risk group]). Similar results were obtained with stratification by age and platelets ($P = .03$).

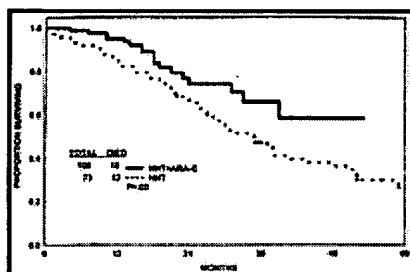


Fig 3. Survival with HHT with or without

View larger version (14K):

[in this window]

[in a new window]

We also analyzed all 173 patients in a multivariate analysis to investigate possible associations of pretreatment characteristics with survival, and we included therapy (HHT v HHT plus ara-C) as a prognostic variable. The multivariate analysis selected older age ($P = .01$), splenomegaly ($P < .01$), and thrombocytosis ($P = .02$) as independent poor significant factors, but therapy remained an important prognostic factor ($P = .026$) favoring the addition of ara-C.

► DISCUSSION

The combination of HHT and ara-C in patients who had experienced treatment failure with IFN α yielded encouraging results. Among patients treated in chronic phase, 72% achieved CHR; 31% achieved a cytogenetic response, which was major in 14%.

Considering that the study group included mostly IFN α -resistant patients in late chronic phase who had few therapeutic options available, the median duration of disease control of 10 months and estimated 4-year survival rate of 55% were favorable. Our results suggest that HHT-based regimens may be effective therapies for patients for whom IFN α therapy was unsuccessful and who are not candidates for allogeneic SCT. They also indicate a potential role of HHT and ara-C as part of front-line CML therapy to improve the degree and duration of cytogenetic response and the prognosis of patients with CML. Considering the acceptable toxicity profile of the regimen, such investigational strategies may be appropriate.

Comparable or even better results have also been reported by Ernst et al,³⁶ who used HHT 2.5 mg/m² daily and ara-C 7.5 mg/m² daily by continuous infusion for up to 14 days. In their report, the CHR rate among 44 patients treated was 93%, and cytogenetic responses were observed in 16 (44%) of 36 patients treated for at least 6 months. Their study group included 14 patients in early chronic-phase CML: all 14 (100%) achieved CHR, and 11 (84%) of 13 assessable patients had a major

- ▲ TOP
- ▲ ABSTRACT
- ▲ INTRODUCTION
- ▲ PATIENTS AND METHODS
- ▲ RESULTS
- DISCUSSION
- ▼ REFERENCES

cytogenetic response. It is not clear how much prior IFN α therapy these patients had received and whether they were clearly IFN α -resistant or had been entered onto the study because of unacceptable IFN α -related toxicities. The comparison of response rates within similar patient subcategories would be of interest. Their study suggested that even better CHR and cytogenetic response rates may be expected depending on patient selection (eg, IFN α toxic patients, early chronic-phase CML), as had also been observed in our previous study of HHT (six courses followed by IFN α maintenance) in early chronic-phase CML.²²

An important question is the additional benefit of ara-C combined with HHT. Although we attempted to compare the two sequential studies at our institution (HHT alone in 73 patients with active disease [21 of whom had clonal evolution] and the current study with HHT plus ara-C), the comparison and evaluation of the benefit from addition of ara-C was difficult because of differences in the study groups (Table 7), dose schedules, and follow-up times. HHT alone was used for 10 to 14 days during remission induction and for 7 days every month during maintenance therapy. Patients previously treated with HHT alone had been less heavily pretreated with IFN α and had not been exposed to either HHT or to ara-C. However, it seems that the HHT plus ara-C combination was not associated with an increased risk of known or unpredictable side effects and may have improved outcome in CML after accounting for known differences in prognostic factors within the two study groups. The possible beneficial effect of ara-C on survival may be mediated through suppression of clones responsible for disease transformation.

Two issues, if resolved, may expand the potential use of HHT in hematologic and perhaps solid tumors: (1) the route-scheduled delivery, and (2) the mechanisms underlying the cardiovascular side effects with shorter infusion schedules. The continuous-infusion schedule, although effective against CML, is cumbersome and limits the investigation of even lower-dose longer-exposure schedules (eg, 0.5 to 1 mg/m² for 3 to 4 weeks). A safe subcutaneous schedule may allow reinvestigating HHT, not only in CML, but also as maintenance therapy in AML, as differentiation therapy in APL, and as a chronic subcutaneous low-dose schedule in MDS. All of these are diseases in which HHT investigations had been discouraged because of the HHT toxicity profile, despite evidence of efficacy.^{17-20,37} Understanding the etiology of the cardiovascular problems may allow a targeted development of a new generation of HHT derivatives designed to avoid cardiovascular side effects and to expand the spectrum of antitumor activity (as has been shown for deoxynucleoside cytidine analogs, eg, ara-C v gemcitabine). This will then rejuvenate anticancer research with HHT-like molecules.

HHT has shown activity in hematologic cancers other than CML and AML that needs further exploration. Low-dose harringtonine was reported to induce remissions in APL.³⁷ Ten patients with APL received harringtonine 1 to 3 mg over 4 to 5 hours daily until complete response; seven (70%) achieved complete response after a median of 71 days and a median cumulative dose of 136 mg. HHT has already shown *in vitro* effects on apoptosis and differentiation,^{26,27,38} which may prove helpful not only against APL but also against other cancers where maturation arrest is pathophysiologic, such as MDS. Among 15 patients with MDS treated by Feldman et al,¹⁹ four (27%) achieved objective responses. Myelosuppressive complications were significant at the dose schedule used (5 mg/m² by continuous infusion daily for 9 days), and a high mortality rate precluded further investigations with this schedule.¹⁹ Lower dose schedules of HHT, as in CML, may prove effective and less toxic in these conditions.

Recent studies have reported encouraging results with a new *BCR-ABL* tyrosine kinase inhibitor, STI-571. Among patients treated in chronic-phase CML who had experienced treatment failure with IFN α (because of resistance or toxicity), the CHR rate was 100% when STI-571 was given at 300 mg or more orally

daily; cytogenetic responses were also observed. STI-571 was also beneficial in the treatment of accelerated-blastic phases of CML.^{39,40} Future studies will better define the relative benefits of STI-571 and HHT plus ara-C, alone or in combinations, in patients who have been treated unsuccessfully with IFN α .

In summary, the combination of HHT and low-dose ara-C was safe and effective in the dose schedule used in our study in patients with late chronic-phase CML. This now offers such patients (if IFN α treatment had failed) a good treatment option and indicates that further studies with IFN α in front-line CML therapy are warranted.

► REFERENCES

1. Kantarjian HM, O'Brien S, Anderlini P, et al: Treatment of myelogenous leukemia: Current status and investigational options. *Blood* 87:3069-3081, 1996 [Free Full Text]
2. Kantarjian HM, Giles FJ, O'Brien SM, et al: Clinical course and therapy of chronic myelogenous leukemia with interferon-alpha and chemotherapy. *Hematol Oncol Clin North Am* 12:31-80, 1998 [Medline]
3. Goldman JM, Szydlo R, Horowitz MM, et al: Choice of pre-transplant treatment and timing of transplants for chronic myelogenous leukemia in chronic phase. *Blood* 82:2235-2238, 1993 [Abstract]
4. Gratwohl A, Hermans J, Niederwieser D, et al: Bone marrow transplantation for chronic myeloid leukemia: Long-term results—Chronic Leukemia Working Party of the European Group for Bone Marrow Transplantation. *Bone Marrow Transplant* 12:509-516, 1993 [Medline]
5. Hehlmann R, Ansari H, Hasford J, et al: Comparative analysis of the impact of risk profile and of drug therapy on survival in CML using Sokal's index and a newscore: German Chronic Myeloid Leukemia (CML) Study Group. *Br J Haematol* 97:76-85, 1997 [Medline]
6. Kantarjian HM, Smith TL, O'Brien S, et al: Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-alpha therapy. *Ann Intern Med* 122:254-261, 1995 [Abstract/Free Full Text]
7. Guilhot F, Chastang C, Michallet M, et al: Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia: French Chronic Myeloid Leukemia Study Group. *N Engl J Med* 337:223-229, 1997 [Abstract/Free Full Text]
8. Tura S: Cytarabine increases karyotypic response in alpha-IFN treated chronic myeloid leukemia patients: Results of a national prospective randomized trial. *Blood* 92: 317, 1998 (abstr)
9. Kantarjian HM, O'Brien S, Smith T, et al: Treatment of Philadelphia chromosome-positive early chronic phase chronic myelogenous leukemia with daily doses of interferon alpha and low-dose cytarabine. *J Clin Oncol* 17:284-292, 1999 [Abstract/Free Full Text]
10. The Italian Cooperative Study Group on Chronic Myeloid Leukemia: Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med* 330:820-825, 1994
11. Allan NC, Richards SM, Shepherd PC: UK Medical Research Council randomized, multicenter trial of interferon-alpha n1 for chronic myeloid leukaemia: Improved survival irrespective of cytogenetic response—The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukemia. *Lancet* 345:1392-1397, 1995 [Medline]
12. Chronic Myeloid Leukemia Trialists' Collaborative Group: Interferon alfa versus chemotherapy for chronic myeloid leukemia: A meta-analysis of seven randomized trials. *J Natl Cancer Inst* 89:1616-1620, 1997
13. Cephalotaxus Research Coordinating Group: Cephalotaxine esters in the treatment of acute leukemia: A preliminary clinical assessment. *Chin Med J* 2:263-272, 1976 [Medline]
14. Chinese People's Liberation Army 18th Hospital: On the treatment of leukemias: Clinical analysis

▲ TOP
 ▲ ABSTRACT
 ▲ INTRODUCTION
 ▲ PATIENTS AND METHODS
 ▲ RESULTS
 ▲ DISCUSSION
 ▪ REFERENCES

- of 72 cases. *Zhonghua Yizue Zazhi*, 58:163, 1978(abstr)
15. LeghaSS, Keating M, PickettS, et al:Phase I clinical investigation of homoharringtonine. *Cancer Treat Rep* 68:1085-1091, 1984[Medline]
 16. NeidhartJA, Young DC, KrautE, et al:Phase I trial of homoharringtonine administered by prolonged continuous infusion. *CancerRes* 46:967-969, 1986[Abstract]
 17. WarrellRP Jr, Coonley CJ, GeeTS: Homoharringtonine: An effective new drug for remission induction in refractory non-lymphoblastic leukemia. *J Clin Oncol* 3:617-621, 1985[Abstract]
 18. FeldmanE, Arlin Z, AhmedT, et al:Homoharringtonine is safe and effective for patients with acute myelogenous leukemia (I). *Leukemia* 6:1185-1188, 1992[Medline]
 19. FeldmanEJ, Seiter KP, AhmedT, et al:Homoharringtonine in patients with myelodysplastic syndrome(MDS) and MDS evolving to acute myeloid leukemia. *Leukemia* 10:40-42, 1996 [Medline]
 20. KantarjianH, Keating M, McCredieK, et al:Phase II study of homoharringtonine in refractory acute myelogenous leukemia. *Cancer* 63:813-817, 1989[Medline]
 21. O'BrienS, Kantarjian H, KeatingM, et al:Homoharringtonine therapy induces responses in patients with chronic myelogenous leukemia in late chronic phase. *Blood* 86:3322-3326, 1995 [Abstract/Free Full Text]
 22. O'BrienS, Kantarjian H, KollerC, et al:Sequential homoharringtonine and interferon-alpha in the treatment of early chronic phase chronic myelogenous leukemia. *Blood* 93:4149-4153, 1999 [Abstract/Free Full Text]
 23. SokalJ, Beingner SH: Low-dose cytosine arabinoside by subcutaneous infusion in early and advanced chronic granulocytic leukemia. *Blood* 68: 233a, 1986 (abstr)
 24. RobertsonMJ, Tantravahi R, GriffinJD, et al:Hematologic remission and cytogenetic improvement after treatment of stable-phase chronic myelogenous leukemia with continuous infusion of low-dose cytarabine. *Am J Hematol* 43:95-102, 1993[Medline]
 25. KantarjianH, Keating M, EsteyE, et al:Treatment of advanced Philadelphia chromosome-positive chronic myelogenous leukemia with interferon-alpha and low-dose cytarabine. *J Clin Oncol* 10:772-778, 1992[Abstract]
 26. VisaniG, Russo D, OttavianiE, et al:Effects of homoharringtonine alone and in combination with alpha interferon and cytosine arabinoside on in vitro growth and induction of apoptosis in chronic myeloid leukemia and normal hematopoietic progenitors. *Leukemia* 11:624-628, 1997 [Medline]
 27. O'BrienS, Keating A, KantarjianH, et al:Homoharringtonine induces apoptosis in chronic myelogenous leukemia cells. *Blood* 82:555a, 1993 (abstr, suppl 1)
 28. SokalJ, Leong SS, GomezGA: Preferential inhibition by cytarabine of CFU-GM from patients with chronic granulocytic leukemia. *Cancer* 59:197-202, 1987[Medline]
 29. KantarjianHM, Dixon D, KeatingMJ, et al:Characteristics of accelerated disease in chronic myelogenous leukemia. *Cancer* 61:1441-1446, 1988[Medline]
 30. MajlisA, Smith TL, TalpazM, et al:Significance of cytogenetic clonal evolution in chronic myelogenous leukemia. *J Clin Oncol* 14:196-203, 1996[Abstract]
 31. CortesJ, Talpaz M, O'BrienS, et al:Suppression of cytogenetic clonal evolution with interferon alpha therapy in patients with Philadelphia chromosome-positive chronic myelogenous leukemia. *J Clin Oncol* 16:3279-3285, 1998[Abstract]
 32. National Cancer Institute : Guidelines for reporting of adverse drug reactions. Bethesda, MD, Division of Cancer Treatment, National Cancer Institute, 1988
 33. KaplanEL, Meier P: Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 58:457-481, 1958
 34. MantelN: Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 50:163-170, 1966[Medline]
 35. RodriguezJ, Cortes J, SmithTL, et al:Determinants of prognosis in late chronic-phase chronic myelogenous leukemia. *J Clin Oncol* 16:3782-3787, 1998[Abstract]
 36. ErnstTJ, Vance E, AlyeaE III, et al:Homoharringtonine and low-dose Ara-C is a highly effective combination for the treatment of CML in chronic phase. *Blood* 90: 517a, 1997 (abstr, suppl 1)
 37. Jing-SongY, Xiao-Hong W, Guang-HuiF, et al:Small dose harringtonine induces complete remission in patients with acute promyelocytic leukemia. *Leukemia* 2:427-429, 1988[Medline]
 38. BoydAW, Sullivan JR: Leukemic cell differentiation in vivo and in vitro: Arrest of proliferation parallels the differentiation induced by the antileukemic drug harringtonine. *Blood* 6:384-392, 1984

The present invention describes a new method of therapy, its use/application in human and animal diseases and disorders, particularly cancers, leukemias, lymphomas, parasite diseases and therapeutic resistance to other agent, by the subcutaneous mode of administration of a drug based upon harringtonines such as homoharringtonine or harringtonine their salt and tautomeric form eventually combined with one or more chemotherapeutic agents or inhibitor of resistance, using a specifically adapted formulation in which (i) the pH of the formulation or constituted solution for injection ranges between 5.5 and 8.5, (ii) the harringtonines are solution or hydrophilic freeze-dried powder ready-to-reconstitute of buffered salt of homoharringtonine or harringtonine and, (iii) the level of chromatographic purity of harringtonines suitable for pharmaceutical use is higher than 99.7%.

39. DrukerBJ, Talpaz M, RestaD, et al: Clinical efficacy and safety of an ABL specific tyrosinekinase inhibitor as targeted therapy for chronic myelogenous leukemia. Blood 94: 368a, 1999 (abstr, suppl1)
40. DrukerBJ, Kantarjian H, SawyersCL, et al: Activity of an ABL specific tyrosine kinase inhibitor inpatients with BCR-ABL positive acute leukemias, including chronicmyelogenous leukemia in blast crisis. Blood 94: 697a, 1999 (abstr, suppl1)

Submitted January 24, 2000; accepted June 6, 2000.

This article has been cited by other articles:

(Search Google Scholar for Other Citing Articles)



Clinical Cancer Research

► HOME

F. Giles, S. Verstovsek, D. Thomas, S. Gerson, J. Cortes, S. Faderl, A. Ferrajoli, F. Ravandi, S. Kornblau, G. Garcia-Manero, E. Jabbour, S. O'Brien, V. Karsten, A. Cahill, K. Yee, M. Albitar, M. Sznol, and H. Kantarjian

Phase I Study of Cloretazine (VNP40101M), a Novel Sulfonylhydrazine Alkylating Agent, Combined with Cytarabine in Patients with Refractory Leukemia

Clin. Cancer Res., November 1, 2005; 11(21): 7817 - 7824.

[Abstract] [Full Text] [PDF]



the Oncologist

► HOME

R. M. Stone

Optimizing Treatment of Chronic Myeloid Leukemia: A Rational Approach

Oncologist, June 1, 2004; 9(3): 259 - 270.

[Abstract] [Full Text] [PDF]



blood

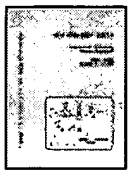
► HOME

H. M. Kantarjian, M. Talpaz, S. O'Brien, F. Giles, G. Garcia-Manero, S. Faderl, D. Thomas, J. Shan, M. B. Rios, and J. Cortes

Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia

Blood, January 15, 2003; 101(2): 473 - 475.

[Abstract] [Full Text] [PDF]



HEMATOLOGY

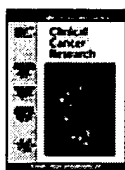
► HOME

B. J. Druker, S. G. O'Brien, J. Cortes, and J. Radich

Chronic Myelogenous Leukemia

Hematology, January 1, 2002; 2002(1): 111 - 135.

[Abstract] [Full Text]



Clinical Cancer Research

HOME

H. M. Kantarjian, S. O'Brien, J. E. Cortes, T. L. Smith, M. B. Rios, J. Shan, Y. Yang, F. J. Giles, D. A. Thomas, S. Faderl, G. Garcia-Manero, S. Jeha, W. Wierda, J.-P. J. Issa, S. M. Kornblau, M. Keating, D. Resta, R. Capdeville, and M. Talpaz

Treatment of Philadelphia Chromosome-positive, Accelerated-phase Chronic Myelogenous Leukemia with Imatinib Mesylate

Clin. Cancer Res., July 1, 2002; 8(7): 2167 - 2176.

[Abstract] [Full Text] [PDF]



Blood

HOME

H. M. Kantarjian, J. Cortes, S. O'Brien, F. J. Giles, M. Albitar, M. B. Rios, J. Shan, S. Faderl, G. Garcia-Manero, D. A. Thomas, D. Resta, and M. Talpaz

Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase

Blood, May 15, 2002; 99(10): 3547 - 3553.

[Abstract] [Full Text] [PDF]



Blood

HOME

M. Talpaz, R. T. Silver, B. J. Druker, J. M. Goldman, C. Gambacorti-Passerini, F. Guilhot, C. A. Schiffer, T. Fischer, M. W. N. Deininger, A. L. Lennard, A. Hochhaus, O. G. Ottmann, A. Gratwohl, M. Baccarani, R. Stone, S. Tura, F.-X. Mahon, S. Fernandes-Reese, I. Gathmann, R. Capdeville, H. M. Kantarjian, and C. L. Sawyers

Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study

Blood, March 15, 2002; 99(6): 1928 - 1937.

[Abstract] [Full Text] [PDF]



The NEW ENGLAND JOURNAL of MEDICINE

HOME

H. Kantarjian, C. Sawyers, A. Hochhaus, F. Guilhot, C. Schiffer, C. Gambacorti-Passerini, D. Niederwieser, D. Resta, R. Capdeville, U. Zoellner, M. Talpaz, B. Druker, and the International STI571 CML Study Group

Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia

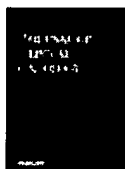
N. Engl. J. Med., February 28, 2002; 346(9): 645 - 652.

[Abstract] [Full Text] [PDF]

JOURNAL OF CLINICAL ONCOLOGY

HOME

F. J. Giles, G. Garcia-Manero, J. E. Cortes, S. D. Baker, C. B. Miller, S. M.



O'Brien, D. A. Thomas, M. Andreeff, C. Bivins, J. Jolivet, and H. M. Kantarjian

Phase II Study of Troxacitabine, a Novel Dioxolane Nucleoside Analog, in Patients With Refractory Leukemia

J. Clin. Oncol., February 1, 2002; 20(3): 656 - 664.

[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

This Article

- ▶ **Abstract** **FREE**
- ▶ **Full Text (PDF)**
- ▶ **Alert me when this article is cited**
- ▶ **Alert me if a correction is posted**

Services

- ▶ **Email this article to a colleague**
- ▶ **Similar articles in this journal**
- ▶ **Similar articles in PubMed**
- ▶ **Alert me to new issues of the journal**
- ▶ **Save to my personal folders**
- ▶ **Download to citation manager**

Google Scholar

- ▶ **Articles by Kantarjian, H. M.**
- ▶ **Articles by O'Brien, S.**
- ▶ **Articles citing this Article**

PubMed

- ▶ **PubMed Citation**
- ▶ **Articles by Kantarjian, H. M.**
- ▶ **Articles by O'Brien, S.**

[About JCO](#)

[Editorial Roster](#)

[Advertising Information](#)

[Rights & Permissions](#)

Copyright © 2000 by the American Society of Clinical Oncology, Online ISSN: 1527-7755. Print ISSN: 0732-183X

[Terms and Conditions of Use](#)



HighWire Press™ assists in the publication of JCO Online

Search for: Limit by:

Browse by Topic or Issue

[Home](#)[Search/Browse](#)[Subscriptions](#)[PDA Services](#)[E-mail Alerts](#)[Custor](#)Institution: **US PATENT & TRADEMARK OFFICE** Sign In as Member/IndividualJournal of Clinical Oncology, Vol 3, 617-621, Copyright ©
1985 by American Society of Clinical Oncology

ARTICLES

Homoharringtonine: an effective new drug for remission induction in refractory nonlymphoblastic leukemia

RP Warrell Jr, CJ Coonley and TS Gee

Homoharringtonine (HHT) is a new plant alkaloid originally isolated in the People's Republic of China. Preliminary studies have suggested antitumor activity in several neoplastic diseases. We treated 49 patients with relapsed or resistant acute leukemia with escalating doses of homoharringtonine administered by continuous infusion. Three dose levels were examined: 5 mg/m² for seven days, 7 mg/m² for seven days, and 5 mg/m² for nine days. Of 28 patients with acute nonlymphoblastic leukemia who received cumulative doses of 45 to 49 mg/m², seven patients (25%) achieved complete remission. Four of these remissions occurred in a subset of ten patients previously resistant to two or more induction attempts with conventional chemotherapy. There were no remissions in three patients with secondary leukemia or in seven patients with acute lymphoblastic leukemia. Reversible hypotension, fluid retention, diarrhea, and tumor lysis syndrome were the major toxic effects of this treatment. Our results indicate that homoharringtonine is an effective new drug for the treatment of acute nonlymphoblastic leukemia and that this drug does not share cross-resistance with conventional antileukemic agents. The recommended dose is 5 mg/m²/d administered by continuous infusion for nine days.

This Article

- ▶ Full Text (PDF)
- ▶ Alert me when this article is cited
- ▶ Alert me if a correction is posted

Services

- ▶ Email this article to a colleague
- ▶ Similar articles in this journal
- ▶ Similar articles in PubMed
- ▶ Alert me to new issues of the journal
- ▶ Save to my personal folders
- ▶ Download to citation manager
- ▶ Cited by other online articles

Google Scholar

- ▶ Articles by Warrell, R. P.
- ▶ Articles by Gee, T. S.
- ▶ Articles citing this Article

PubMed

- ▶ PubMed Citation
- ▶ Articles by Warrell, R. P., Jr
- ▶ Articles by Gee, T. S.

This article has been cited by other articles:

(Search Google Scholar for Other Citing Articles)

JOURNAL OF CLINICAL ONCOLOGY

▶ HOME

H. M. Kantarjian, M. Talpaz, T. L. Smith, J. Cortes, F. J. Giles, M. B. Rios,
S. Mallard, J. Gajewski, A. Murgo, B. Cheson, and S. O'Brien



Search

[Advanced Scholar Search](#)
[Scholar Preferences](#)
[Scholar Help](#)

Scholar Results 1 - 10 of about 11 citing **Warrell: Homoharringtonine: an effective new drug for remission**

Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic

...
HM Kantarjian, M Talpaz, TL Smith, J Cortes, FJ ... - J Clin Oncol, 2000 - jco.org
Search for: Limit by: All Topics ...
Cited by 34 - [Web Search](#) - [jco.org](#) - [ncbi.nlm.nih.gov](#)

History, Current Research, and Future Directions

HM Kantarjian, M Talpaz, V Santini, A Murgu, B ... - CANCER, 2001 - doi.wiley.com
Page 1. Homoharringtonine History, Current Research, and Future Directions
Hagop M. Kantarjian, MD 1 Moshe Talpaz, MD 1 Valeria Santini ...
Cited by 17 - [Web Search](#) - [doi.wiley.com](#) - [ncbi.nlm.nih.gov](#)

In vitro effects of STI 571-containing drug combinations on the growth of Philadelphia-positive

...
B Scappini, F Onida, HM Kantarjian, L Dong, S ... - Cancer, 2002 - doi.wiley.com
Page 1. In Vitro Effects of STI 571-Containing Drug Combinations on the Growth
of Philadelphia-Positive Chronic Myelogenous Leukemia Cells ...
Cited by 15 - [Web Search](#) - [ncbi.nlm.nih.gov](#)

Simultaneous homoharringtonine and interferon-in the treatment of patients with chronic-phase

...
SO'Brien, M Talpaz, J Cortes, J Shan, FJ Giles, ... - Cancer, 2002 - doi.wiley.com
Page 1. Simultaneous Homoharringtonine and Interferon- in the Treatment
of Patients with Chronic-Phase Chronic Myelogenous Leukemia ...
Cited by 13 - [Web Search](#) - [doi.wiley.com](#) - [ncbi.nlm.nih.gov](#)

A phase II study of homoharringtonine for the treatment of children with refractory or recurrent

...
BA Bell, MN Chang, HJ Weinstein - Medical and Pediatric Oncology, 2001 - doi.wiley.com
Page 1. Med Pediatr Oncol 2001;37:103±107 A Phase II Study of Homoharringtonine
for the Treatment of Children With Refractory or Recurrent Acute Myelogenous ...
Cited by 6 - [Web Search](#) - [doi.wiley.com](#) - [ncbi.nlm.nih.gov](#)

Etoposide-resistant human colon and lung adenocarcinoma cell lines exhibit sensitivity to ...

LJ Wilkoff, EA Dulmadge, G Vasanthakumar, JP ... - Cancer Chemotherapy and Pharmacology, 1993 -
springerlink.com
Page 1. Cancer Chemother Pharmacol (1993) 33: 149-153 cancer chemotherapy
and pharmacology 9 Springer-Verlag 1993 Etoposide-resistant ...
Cited by 3 - [Web Search](#) - [ncbi.nlm.nih.gov](#)

Promising approaches in acute leukemia

J Cortes, HM Kantarjian - Investigational New Drugs, 2000 - kluweronline.com
Page 1. Investigational New Drugs 18: 57-82, 2000. © 2000 Kluwer Academic
Publishers. Printed in the Netherlands. 57 Invited review ...
Cited by 1 - [Web Search](#) - [springerlink.com](#) - [ncbi.nlm.nih.gov](#)

Metabolism of homoharringtonine, a cytotoxic component of the evergreen plant Cephalotaxus

...

D Ni, DH Ho, M Vijeswarapu, E Felix, P Robyn Rhea ... - Journal of Experimental Therapeutics and Oncology, 2003 - blackwell-synergy.com
Full Article. View/Print PDF article (151K). Download to reference manager.
Journal of Experimental Therapeutics and Oncology Volume ...
[Cited by 1](#) - [Web Search](#) - [ingentaconnect.com](#) - [ncbi.nlm.nih.gov](#)

Homoharringtonine mediates myeloid cell apoptosis via upregulation of pro-apoptotic bax and inducing ...

L Yinjun, J Jie, X Weilai, T Xiangming - American Journal of Hematology, 2004 - doi.wiley.com
Page 1. Homoharringtonine Mediates Myeloid Cell Apoptosis via Upregulation of Pro-apoptotic bax and Inducing Caspase-3-Mediated Cleavage of Poly(ADP-ribose) ...
[Cited by 1](#) - [Web Search](#) - [ncbi.nlm.nih.gov](#)

Adult Acute Myeloid Leukemia

TO Overview - [jncicancerspectrum.oupjournals.org](#)
Content Sources... ...
[Web Search](#)

Google ►

Result Page: 1 2 [Next](#)

[Google Home](#) - [About Google](#) - [About Google Scholar](#)

©2006 Google

[Generate Collection](#)[Print](#)**Search Results - Record(s) 1 through 3 of 3 returned.**

☐ 1. [20040006064](#). 01 Apr 03. 08 Jan 04. Cephalotaxanes, their method of preparation and their use in treatment of cancers, leukemias, parasites including those resistant to usual chemotherapeutic agents and as reversal agents. Robin, Jean-Pierre, et al. [514/214.01](#); 540/579 A61K031/55 C07D487/02.

☐ 2. [20020128258](#). 09 Mar 01. 12 Sep 02. Therapeutical method involving subcutaneous administration of drugs containing cephalotaxine derivatives. Robin, Jean-Pierre, et al. [514/214.01](#); A61K031/55.

☐ 3. [H000271](#). 18 Dec 85; 05 May 87. Treatment of malaria with esters of cephalotaxine. Whaun; June M.. [514/214.01](#); A61K031/55 .

[Generate Collection](#)[Print](#)

Terms	Documents
L3 and (purity or pure or dosage or conc or concentration) adj5 (hht or homoharringtonine)	3

[Prev Page](#)[Next Page](#)[Go to Doc#](#)



Application
Number

SEARCH

IDS Flag Clearance for Application

10617927

IDS
Information

Content	Mailroom Date	Entry Number	IDS Review	Reviewer
M844	09-07-2004	17	<input checked="" type="checkbox"/>	01-30-2006 08:46:51 HLilling

UPDATE

STN

FILE 'WPIDS, CAPLUS, USPATFULL, IFIPAT, TOXCENTER, DRUGU, BIOSIS, PASCAL'
ENTERED AT 03:52:18 ON 30 JAN 2006

L4

14 S L3

L5

8 DUP REM L4 (6 DUPLICATES REMOVED)

ANSWERS '1-3' FROM FILE WPIDS

ANSWER '4' FROM FILE CAPLUS

ANSWERS '5-6' FROM FILE USPATFULL

ANSWER '7' FROM FILE TOXCENTER

ANSWER '8' FROM FILE DRUGU